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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/817,306 | 04/02/2004 | Chandrashekhar Kocherlakota | U 014533-9 | 1835 |

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| EXAMINER | |
|---|---|
| SASAN, ARADHANA | |
| ART UNIT | PAPER NUMBER |
| 1609 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/10/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/817,306 | KOCHERLAKOTA ET AL. | |
| | Examiner | Art Unit | |
| | Aradhana Sasan | 1609 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/02/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. Claims 1-13 are being presented for examination.

### *Information Disclosure Statement*

2. The information disclosure statement (IDS) submitted on 06/02/2004 was filed. The submission is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statement. See attached copy of PTO-1449.

### *Specification*

3. The disclosure is objected to because of the following informalities:

On page 12, [0057], the terms "and stabilizer.on, or both and (iii)" is unclear and confusing.

On page 22, [0091], under dissolution condition, "PH" should be "pH".

On page 23, [0095], the comparison of dissolution data is not presented.

On page 23, [0096], " F)" should be in lower case, i.e. " f)" to be consisted with the rest of the bullets.

Appropriate correction is required.

### *Claim Objections*

4. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims

are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Instant claims 11 and 12 should be renumbered as 10 and 11 respectively.

5. Claims 6 and 7 objected to because of the following informalities: "1-methyl-2-pyrrolidone" is misspelled as "1-methyl-2-pyrrolidine". Appropriate correction is required.

6. Claims 4 and 5 objected to because of the following informalities: The limitations of three parts of the composition are recited, however only (iii) is designated. The claims should include the designations (i) and (ii) before the drug phase and the co-solvent phase respectively. Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858).

The claimed invention is a self micro-emulsifying composition comprising etoposide encapsulated in a capsule shell. The composition comprises (i) a drug phase comprising etoposide and a solvent, (ii) a co-solvent, and (iii) an emulsifying base comprising a lipid, a surfactant, and a stabilizer.

Begum et al. teaches a liquid dosage form of etoposide to be administered in capsule form (Abstract). The liquid dosage "composition with etoposide results in markedly improved absorption of the drug following ingestion of the composition. It is believed that this is due to the formation of a micellar solution of etoposide on dilution thereof with the gastric contents" (Col. 2, lines 14-18). The etoposide is mixed with a solvent polyethanol glycol 300 and the composition includes citric acid (Col. 5, lines 5-10).

Begum et al. does not teach a self-microemulsifying composition comprising etoposide.

Crison et al. (US 5,993,858) teaches a self-microemulsifying formulation for increasing the bioavailability of a drug, which includes an emulsion including an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant (Abstract). The preferred HLB range for the hydrophilic co-surfactant is between approximately 10 and 14 (Col. 4, lines 31-33). The co-surfactants used include LABRASOL (Gattefosse Corporation), which are caprylocaproyl macrogolglycerides, LABRAFAC (Gattefosse Corporation) which are medium chain triglycerides, glycerylesters, fatty acid esters, and polyoxyethylene derivatives (Col. 4, lines 4-14, and lines 37-40).

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the liquid etoposide composition of Begum with the self-microemulsifying formulation of Crison. The motivation to combine these references is provided by the teaching that these compositions can form microemulsions "when exposed to gastrointestinal fluids" (Col. 2, lines 16-18). The self-microemulsifying

composition would provide "a method of increasing dissolution and bioavailability of ... poorly water-soluble drugs..." (Col. 2, lines 48-51).

9. Claims 3-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Begum et al. (US 4,713,246), in view of Crison et al. (US 5,993,858), and further in view of Kaplan et al. (US 4,772,589) and Hauer et al. (US 5,342,625).

The teachings of Begum and Crison are stated above.

Begum and Crison do not teach 1-methyl-2-methylpyrrolidone or dimethyl isosorbide as solvents of etoposide and the specific components of the emulsifier base.

Kaplan et al. (US 4,772,589) teaches a stable solution of etoposide in 1-methyl-2-pyrrolidinone, and solutions having etoposide concentration as high as 500 mg/ml used to fill gelatin capsules (Abstract). Kaplan also discloses dimethylisosorbide as a possible solvent for etoposide (solubility 320 mg/ml) (Col. 3, Table III).

Hauer et al. (US 5,342,625) teaches pharmaceutical compositions of cyclosporins in microemulsion form. The preferred ether components used in the composition include glycofurol (Col. 14, lines 29-33). The composition contains surfactant, co-solvents or thickening agents (Col. 14, lines 33-35). Hauer teaches polyalkylene glycol ethers (Col. 11, lines 59-63). Also taught are lipids, "propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate," and "propylene glycol caprylic-capric acid diester" (Col. 10, lines 60-68). Fatty acid triglycerides, ... medium chain triglycerides, and neutral plant oils are also taught (Col. 8, lines 65-68). Surfactants such as sorbitan fatty acid esters (propylene glycol laurate, are taught (Col.

11, lines 53-58). Furthermore, Hauer teaches anti-oxidants in the composition, "in particular, a tocopherol, is particularly advantageous" (Col. 13, lines 44-50).

A person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the liquid etoposide composition of Begum with the self-microemulsifying formulation of Crison, and further combine the etoposide solvent teaching of Kaplan. The motivation to use the Kaplan reference is provided by the fact that "etoposide is suitably stable in NMP" (n-methyl-pyrrolidone or 1-methyl-2-pyrrolidone) (Col. 2, line 66). The co-solvent glycofurol is taught by Hauer and would be an obvious alternative as a co-solvent for etoposide, which a poorly soluble drug. Also, the co-solvent diethyleneglycol-mono-ethylether is a polyalkylene glycol ether and would be obvious to one skilled in the art. The solvents, co-solvents, lipids, surfactants, and stabilizers of the claimed invention are known in the art and a person could choose the components according to the desired release profile, bioavailability and stability.

Regarding instant claims 4 and 5, which recite the weight percentages of etoposide, solvent, co-solvent, and emulsifying base, a person skilled in the art would modify the percentages of the composition based on the required dosage and desired release profile, and the recited percentages are obvious variants unless there is evidence of criticality or unexpected results.

Regarding instant claim 11, Kaplan teaches etoposide and N-methyl-pyrrolidone. Hauer teaches diethyleneglycol monoethyl ether, plant oils (instant claim recites polyoxyl 35 castor oil), polyoxyethylene-sorbitan-fatty acid esters (TWEEN) (instant claim recites polysorbate 20), and propylene glycol mono- and di-fatty acid esters such

as propylene glycol dicaprylate. Crison teaches medium chain triglycerides, caprylocaproyl macrogolglycerides, and glyceryl esters. Therefore, all the claim limitations are taught by the references and would be obvious to one skilled in the art.

Regarding instant claims 12, Begum in view of Kaplan teaches etoposide, citric acid, and n-methyl-pyrrolidone. Hauer teaches diethyleneglycol monoethyl ether, plant oils (instant claim recites polyoxyl 35 castor oil), polyoxyethylene-sorbitan-fatty acid esters (TWEEN) (instant claim recites polysorbate 20). Therefore, all the claim limitations are taught by the references and would be obvious to one skilled in the art.

***Conclusion***

1. No claims are allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CECILIA TSANG
SUPERVISORY PATENT EXAMINER